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Emergence of New Delhi metallo-β-lactamase type 1-producing *Enterobacteriaceae* and non-*Enterobacteriaceae*: global case detection and bacterial surveillance

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SUMMARY

Objective: A systematic review of the literature was conducted to summarize the descriptive and molecular epidemiology of human cases and surveillance reports with New Delhi metallo-β-lactamase type 1 (NDM-1)-producing bacteria reported worldwide from January 2008 through July 6, 2011.
Methods: A comprehensive literature review was conducted to identify publications of NDM-1-producing bacteria. Studies were divided into two broad categories of (1) case series and case reports of NDM-1-producing bacteria, or (2) active surveillance and environmental surveillance studies of NDM-1-producing bacteria.
Results: Sixty cases with NDM-1-producing bacteria were reported in the 3.5-year interval since the index case detection. The majority of reported cases represented colonization without evidence of infection (n = 39, 65%); urine was the most common specimen source for cases with infection (41.7%) and colonization (33.3%). Seventeen cases (28.3%) had NDM-1-producing bacteria at more than one body site. *Klebsiella pneumoniae* and *Escherichia coli* were the most frequent bacteria detected, and the multilocus sequence type data from 34 *E. coli* and *K. pneumoniae* clinical isolates provided an incomplete, yet heterogeneous global distribution of NDM-1-producing bacteria. The majority of cases (63.3%) had exposure to the Indian subcontinent of south central Asia, and laboratory surveillance systems, as well as an environmental survey from India, suggest a presence of environmental reservoirs for potential human infection and colonization with NDM-1-producing bacteria.
Conclusions: The majority of case reports with NDM-1-producing bacteria had presumed colonization, not infection, with one or more bacteria. The available human case reports and surveillance data suggest a global distribution of NDM-1-producing *Enterobacteriaceae* and non-*Enterobacteriaceae*.

1. Introduction

Infections with multidrug-resistant Gram-negative bacteria are of major global concern given limited therapeutic options, untoward clinical outcomes, and excess costs of care.[1,2] Heterogeneous resistance trends to cephalosporins, fluoroquinolones, and carbapenems exist among *Enterobacteriaceae* and non-*Enterobacteriaceae*, which add to the complexity of region-specific effective infection prevention and treatment strategies. Treatment of carbapenemase-resistant *Enterobacteriaceae* (CRE) now includes combination regimens of carbapenems, colistin, aminoglycosides, aztreonam, and tigecycline, as well as prolonged infusions of carbapenems.[3–11] Gram-negative bacteria with the New Delhi metallo-β-lactamase type-1 (NDM-1), produced by the bla_{NDM-1} gene, utilize at least one zinc atom at the active site to facilitate hydrolysis of a broad variety of β-lactams and carbapenems.[12] The epidemiology of NDM-1 is compounded by interspecies dispersion and recognized implications for patient care, public health, antimicrobial surveillance programs, and drug development.[3,8,13–15]

Initial case detection of NDM-1 production was characterized in a clinical urinary isolate of *Klebsiella pneumoniae* from a 59-year-old man who returned to Sweden after hospitalization in India in January 2008.[16] This patient was concurrently colonized with an NDM-1-producing *Escherichia coli* in the stool.[16] Subsequently, two NDM-1-producing *E. coli* strains from 2006 were retrospectively identified in stored clinical isolates from healthcare facilities in New Delhi, India via the SENTRY Antimicrobial Surveillance Program.[17] Since 2008, NDM-1-producing bacteria have been reported via case detection, active and passive laboratory surveillance systems, national surveillance programs, and

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environmental surveillance studies.[7,17–23] The most frequent detection of NDM-1 has been in *K. pneumoniae* and *E. coli*, with global spread associated with international travel, medical tourism, and potential exposures in the Balkan region and the Indian subcontinent.[3,16,18,20,22,24–26] In Europe, a case series of subjects with NDM-1-producing *Enterobacteriaceae* has served as a template for linking clinical and laboratory case detection.[7] From an epidemiological perspective, the global burden of disease associated with NDM-1-producing pathogens remains underrepresented in the literature.[3,27] The objective of this systematic review was to characterize the global distribution of human cases and surveillance studies for NDM-1-producing bacteria for the 3.5-year period since the initial case detection.

2. Methods

2.1. Systematic literature review

A comprehensive literature review was conducted using the PubMed search engine and the following key search terms: "New Delhi Metallo-Beta-Lactamase" and "NDM-1". Search terms were limited to publications in the English language, publications in humans, and literature sources published from January 2008 (month and year of the clinical presentation of the NDM-1 index case) through July 6, 2011. Articles available through online advanced access were included and, in order to ascertain any citations that were not identified in the original literature search, relevant publications were examined for additional references to NDM-1-producing bacteria. Articles with complete text were analyzed and the relevant data from these publications were systematically collated into a tabulated format. Articles with only abstracts were included if the abstract contained sufficient information to meet the study inclusion criteria. NDM-1 publications were divided into two broad categories of either (1) case series and case reports of NDM-1-producing bacteria, or (2) active surveillance or environmental surveillance studies of NDM-1-producing bacteria. When additional information of interest for the systematic data collection was not in the publication, we attempted to contact the respective corresponding author to gather or to discern additional descriptive information for inclusion in the systematic review. Additional relevant data for 35 cases were obtained from corresponding authors of the original publications. Subsequent to the initial review of publications, we conducted a second structured literature search to assure capture of active laboratory surveillance programs and environmental surveillance studies of NDM-1-producing pathogens worldwide. This second literature review was conducted using the same search limits as the initial PubMed search with the following key search terms: "New Delhi metallo-β-lactamase", "NDM-1", "surveillance study", and "environmental study". This search did not yield any additional NDM-1 surveillance or environmental studies.

2.2. Reported cases: data collection and study definitions

A case was defined as a patient for whom at least one clinical isolate of NDM-1-producing bacteria had been isolated, confirmed, and reported in the published literature. Demographic, clinical, and microbiological data were systematically collected from the case reports and case series. The demographic data included age, gender, and geographic location at the time of the NDM-1 specimen procurement. Exposure to the Indian subcontinent of south central Asia was defined as 'yes' for residence, travel, medical care, or hospitalization, or 'no' for either lack of exposure or uncertain for exposure. The clinical data included comorbid conditions, clinical status at hospital discharge or at last follow-up, recent travel history within 1 year prior to detection of NDM-1, contact with other healthcare facilities, prior medical treatment or procedures, length of stay at the medical facility abroad, inter-country transfer, and any local transmission events with known contact of a travel-associated case. Microbiological data included the date of specimen collection, the bacterial species harboring NDM-1, specimen source(s) for both infected and colonized NDM-1 cases, and the multilocus sequence type (MLST), when available in the published literature. The MLST is a nucleotide sequence-based approach for the unambiguous characterization of bacterial isolates. Additional descriptive and microbiological data, if available, were also reviewed. Each reported case was categorized as either infection or presumed colonization. A case infection was defined as a report of NDM-1-producing bacteria in either (1) blood or another sterile body fluid specimen, or (2) clinical culture specimens from potentially non-sterile specimen sources such as the respiratory tract, wounds, urine, and other sources that were deemed to be associated with infection by the clinical investigative team. Cases with infection were further reviewed to determine if the infected case was also colonized with one or more NDM-1-producing bacteria, and if confirmed for colonization, the identified source(s) of colonization. A case of presumed colonization with NDM-1-producing bacteria was either (1) asymptomatic, (2) deemed to be colonized and without infection by the investigator/authors in either the initial report or follow-up correspondence, or (3) uncertain for infection or colonization by the original investigators, or if the author did not confirm colonization by personal communication, the case was categorized as presumed colonization. Specimens identified as urinary catheter, skin, and nose were categorically grouped as 'other' sources, and the source 'wound' included isolates from pus.

2.3. Laboratory and surveillance studies: data collection and study definitions

Identified surveillance studies for NDM-1-producing bacteria were assessed for geographic location of the patient at the time the clinical isolate was procured. Data included specimen source, date of specimen collection, number of NDM-1 isolates detected for each case, bacterial species, and when available, the MLST. The type of surveillance program, target pathogens, and denominator definitions were systematically recorded, given the variation in the laboratory detection methodologies and surveillance programs. The proportion of NDM-1-producing bacteria reported in each of these studies was contingent upon the criteria for screening restricted to either Gram-negative bacteria, *Enterobacteriaceae*, or CRE. All data were entered into Microsoft Excel for descriptive statistics and summary calculations.

3. Results

3.1. Literature review for case reports, case series, and surveillance studies

The systematic literature review yielded 94 publications with reports of NDM-1-producing bacteria published in print or online between January 2008 and July 6, 2011 and limited to humans and articles in English. Thirty-six publications were case reports or case series,[16,18,21,24,28–59] and nine publications were surveillance studies;[3,4,7,23,60–64] 49 publications were excluded. Among excluded publications was the first published case report of NDM-2, a variant form of NDM, and a report on *Acinetobacter baumannii* isolates that lacked pertinent case details.[38,65] After review of the identified publications and citations, an additional six case reports,[20,66–70] two surveillance studies,[17,71] and one Health Protection Agency report regarding carbapenem resistance and NDM-1[19] were included. These publications of NDM-1-producing